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Investigating Adipokine levels in the sera of patients with myocardial infarction in a 6-month follow up

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Abstract

Adipokines are peptides that regulate endothelial function, inflammation, blood pressure, and hemostasis. We measured Leptin, Adiponectin, Resistin and Adipsin in a cohort of 36 STEMI patients. Serum levels of Adipokines were measured in three time-points by a multiplex assay. A significant difference in Adipsin concentration between day-5 (T5) and day-180 (T180) post-MI was observed. Resistin levels decreased significantly from day 0 (T0) to T5 and T180. Adiponectin/Resistin ratio increased from T0 to T180. Leptin at T0 and T5 were higher in non-smokers. Adipsin at T0 was inversely correlated with heart rate, respiratory rate and pulse rate. Adiponectin/Resistin ratio at T180 negatively correlated with respiratory-rate. Adiponectin/Resistin ratio at T180 was higher in patients with grade-1 atrioventricular (AV) block. Anteroseptal hypokinesia (AH) correlated with Resistin at T0 and Adipsin at T5 while Leptin at T0 and T5 correlated with AH. Adiponectin/Resistin ratio at T180 was; however, lower in patients with AH. A decreasing trend in Resistin and its T0 association with AH plus correlation of Leptin at T0 and T5 with AH show the effect of Adipokines on mechanical complications after MI. We suggest that Adipokine networks have both beneficial and harmful effects and may be new cardiac biomarkers and/or drug targets.

Keywords: adipokine, biomarker, inflammation, myocardial infarction

1. Introduction

The rate of cardiovascular diseases in middle- and low-income countries is growing rapidly (1). One of the major cardiovascular pathologies occurs in myocardial infarction (MI) which is the most detrimental atherosclerosis related complication (2). Different risk factors such as stress, hypertension, physical inactivity, obesity, diabetes mellitus and cigarette smoking lead to ischemia, reperfusion injury and MI (3). A complex cascade of inflammatory events results in progression of atherosclerosis, plaque rupture, and emboli in MI. Lymphocyte infiltration is found in MI patients who die immediately, in short (four weeks), or long (four months) time after coronary thrombosis (2).

Adipose tissue, consisted of adipocytes, fibroblasts, lymphocytes, macrophages and other cells, is an active tissue which expresses a number of biologically active molecules named Adipokines (4). It is now well received that obesity, insulin resistance, type 2 diabetes, high blood pressure and cardiovascular (CV) system are highly influenced by the action of Adipokines (5-8). Adipokines are peptides that are produced by Adipocytes, endothelial and immune cells, fibroblasts, and other cells which regulate endothelial function, inflammation, blood pressure, hemostasis, adipogenesis, immune cell migration, adipocyte metabolism and function (9, 4, 10).

Leptin was the first discovered Adipokine in 1994. Administration of Leptin has cardio-protective effects e.g., reduces the extent of myocardial infarction (MI) and protects against reperfusion damage (11). Nevertheless, most studies consider Leptin as a hazardous Adipokine in cardiovascular system that is associated with atherosclerosis, hypertension and the metabolic syndrome. Also, Leptin affects blood pressure, insulin resistance, platelet aggregation and has pro-inflammatory effects (11). Higher levels of Leptin are associated with myocardial infarction (MI) and stroke, independent of traditional risk factors or obesity (11, 12).

Resistin, another Adipokine, is a 12.5-kDa cysteine-rich polypeptide, and a member of the FIZZ (found in inflammatory zones) family of proteins (13). There is a relationship between Resistin and classic mediators of inflammation, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (14). In fact, Resistin has been shown to have pleiotropic functions in metabolism and physiology with roles in inflammation (15), endothelial dysfunction (16) cardiomyocyte function (17), and cholesterol metabolism (18). In vitro experiments have shown that Resistin activates endothelial cells to upregulate the expression of adhesion molecules and inflammatory cytokines, induces proliferation and migration of smooth muscle cells, and accelerates

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transformation of foam cells (19). Therefore, Resistin may contribute to the atherosclerotic process by stimulating multiple pro-atherosclerotic pathways (20). Increased serum Resistin levels are shown to be associated with coronary artery disease (CAD) and the risk of cardiovascular death (21).

Adiponectin, also named as ACRP30 and AdipoQ, is an adipose tissue-derived Adipokine (21, 22). Many Adipokines are positively regulated by adiposity, but adiponectin levels in plasma are negatively regulated by accumulation of body fat (23). Clinical studies implicate hypo-adiponectinemia in the pathogenesis of CAD. Adiponectin plays a protective role in the development of insulin resistance, hypertension and cardiovascular disease (CVD) (24).

Another Adipokine, Adipsin, is mainly expressed in adipocytes and is involved in the activation of the alternative pathway of complement with the acyl-stimulating protein as the final component. The positive correlation between Adipsin levels and body mass suggests the role of Adipsin in the increase of fat mass through acyl-stimulating protein synthesis, increase of differentiation of pre-adipocytes, and synthesis of triglycerides (25). Adipsin level is reduced in murine models of obesity but it either increases or remains unchanged in obese human subjects (26). Despite a large body of data on many Adipokines, the information on the Adipsin and its correlation with MI is scarce. In this study, we measured the serum levels of Leptin, Resistin, Adiponectin, and Adipsin in a cohort of patients with MI in a 6-month follow up and investigated their association with the risk factors and clinical criteria of patients.

2. Materials and methods

2.1. Study population

In this study, a total of 50 individuals with STEMI who developed a first coronary event were recruited. All patients with chest pain complaints, increase in TnT levels and ST elevation in anterolateral and anteroseptal leads, if aged <75 years, were eligible for inclusion in the study. Myocardial infarction was diagnosed based on the presenting electrocardiogram (ECG) in combination with serial TnT measurements. Selective coronary angiography in the hospital course was used to further confirm the diagnosis. Patients with Chronic Renal Failure (CRF), autoimmune diseases, and cardiogenic shock were excluded from the study. All patients were monitored for six months. After six months echocardiography was done for all the patients for evaluation of LV systolic function. LV ejection fraction was assessed by echocardiography performed by a single blinded expert operator. Follow-up end points were defined as a new ACS (e.g. cardiac ischemia and AMI) or a repeat coronary revascularization (PCI and CABG) after the initial event, which were combined as nonfatal events. The fatal events comprised all cases of all-cause mortality. Otherwise, follow-up ended at the date of withdrawal from the study or at six months after entry.

For each patient, demographic and clinical information including age, gender, and history of hypertension (Systolic blood pressure > 150 mmHg and Diastolic blood pressure > 90 mmHg), hyperlypidemia (Total Cholesterol >240 mg/dL or LDL- Cholesterol >160 mg/dL or Triglycerides >200 mg/dL), diabetes mellitus, obesity and BMI, and smoking were obtained and recorded. This datasheet as well as their laboratory data were used for statistical analysis. A resting heart rate between 60 and 100 beats per minute was considered normal. Higher than 100 beats per minute (tachycardia) and lower than 60 beats per minute (bradycardia) were considered not normal. Respiratory rate was recorded as the number of breaths taken per minute. The resting respiration rate of 12 to 20 breaths per minute was considered normal. A respiration rate under 12 or over 25 breaths per minute while resting was considered not normal. The sera were collected at three time points as: 1) On admission (T0) 2) 5th day of hospitalization (T5) 3) 180 days after MI (T180). Of 50 original individuals who consented to enter the study only 36 remained available for the last (T180) sampling. Therefore, the levels of Adipokines were measured in the sera of 36 STEMI patients (24 men and 12 women) in the T0 and T5. In T180, three patients had been expired and therefore, the number of cases decreased to 33 at this time point. All demographic, general and clinical information of the patients were recorded at the time of sampling by collaborating cardiologist.

2.2. Serum separation

Blood samples were drawn from patients and aliquots of serum were collected from each individual at the three time points. The sera were frozen in -40˚C until tested.

2.3. Adipokine multiplex assay

Circulating levels of serum Adiponectin, Resistin, Adipsin, Leptin were determined in three time-points with a commercially available multiplex bioassay (LEGENDplex™ Human Metabolic Panel 1 (4-plex)). The assay was performed according to the manufacturer's specifications. The samples were tested using a FACS Calibur Flow Cytometer (BD) instrument system.

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Table 1. Adipokine levels based on demographical features of AMI patients in each time point

Subjects		No (%)	Adiponectin Mean (SD) (ng/ml ×10^3)			Adipsin Mean (SD) (pg/ml×10^3)			Resistin Mean (SD) (pg/ml ×10^3)			Leptin Mean (SD) (pg/ml ×10^3)		
			T0	T5	T180	T0	T5	T180	T0	T5	T180	T0	T5	T180
No.		36 (100)												
Age (mean ± SD)		58.8±8.6	9.5 (2.5)	1.1 (4.6)	10.9 (2.8)	6.4 (2.6)	1.08 (2.8)	7.8 (4.4)	2.2 (1.5)	1.99 (1.7)	1.1 (8.5)	3.77 (4.4)	3.4 (3.1)	5.8 (3.8)
	#P		0.54	0.12	0.48	0.27	**0.007**	0.24	0.43	0.16	0.46	0.60	0.84	0.84
Gender (M/F)		24/12	9.8 (2.9)/1.0 (2.9)	1.09 (3.7) /1.1 (4.6)	12.2 (9.1) /8.6 (30.7)	8.2 (3.7) /5.2 (2.3)	1.1 (6.8) /9.2 (7.6)	8.8 (6.9) /4.8 (2.4)	2.3 (2.9)/2.5 (1.8)	1.5 (1.18) /2.2 (1.9)	1.09 (9.3) /3.8 (4.4)	3.8 (4.4) /7.04 (6.8)	2.8 (2.8) /7.02 (6.02)	5 (4.2) /5.4 (4.6)
	P		0.6	0.75	0.25	**0.01**	0.14	**0.03**	0.39	0.26	0.95	0.14	**0.03**	0.86
BMI	18.5-24.9	9 (25)	9.6 (3.1)	8.8 (2.7)	12.2 (7.3)	7.6 (2.5)	8.2 (2.17)	7.99 (3.3)	3.4 (4.5)	1.7 (1.3)	0.9 (9.05)	6.2 (6.4)	3.1 (3.8)	3.7 (1.7)
	25-30	10 (27.8)	1.07 (2.2)	1.4 (5.2)	10.3 (3.5)	7.8 (4.9)	1.2 ()7.08	7.3 (4.8)	1.96 (1.7)	2.1 (1.9)	1.02 (6.6)	3.7 (2.5)	5.2 (4.6)	5.07 (4.7)
	>30	1 (2.78)	8.4	1.38	5.5	3.6	1.38	3.7	2.8	1.6	0.5	1.7	5.4	5.1
	Missing	16 (44.4)	9.8 (2.9)	1.04 (2.0)	1.1 (10.3)	6.9 (2.3)	1.04 (8.99)	7.8 (8.1)	2.05 (1.2)	1.6 (1.38)	1.15 (9.77)	4.1 (5.6)	4.08 (5.1)	5.9 (5.1)
	P		0.44	0.06	0.44	0.39	0.17	0.37	0.59	0.79	0.39	0.26	0.43	0.74

Correlation P value between age and Adipokines levels at each time point

2.6. Statistical analysis

Mann-Whitney U test was used for comparing clinical and biochemical variables between groups. To assess differences between in-group variables, Chi-Square test was used. Spearman's correlation coefficients were estimated to determine associations between Adipokine concentrations and anthropometric measurements and biochemical variables. All statistical assessments were considered significant as P-value < 0.05. All analyses were performed using SPSS version 16 (version 9.2; SAS Institute, Cary, NC).

3. Results

The demographical and clinical features of MI patients and Adipokine levels in the groups are shown in tables 1 and 2.

3.1. Concentration of serum Adipokines in the studied time points

There were no significant differences in serum Adiponectin and Leptin concentrations between the three time points in MI patients (P= 0.3 and P= 0.3, respectively; Figure 1). However, a significant difference in serum Adipsin concentration between day 5 (T5) and day 180 (T180) post-MI was observed (P= 0.02, Fig. 1). In addition, there was a significant difference in serum Resistin levels between day 0 (T0) and day 180 (T180) as well as day 5 (T5) and day 180 (T180) (P= 0.0001 and P= 0.009, respectively, Fig. 1). Interestingly, the Adiponectin/Resistin ratio increased from T0 to T180 and the difference between T180 and T0 was significant (P=0.002).

3.2. Concentration of Adipokines in the studied time points based on gender

The serum Resistin concentration at T0 was significantly higher than T180 among women and men (P= 0.004, and P= 0.02, respectively). A trend of decrease in Resistin level in both genders was observed from T0 to T180 as well (Figs. 2A and 2B). Adipsin T180 levels were higher in men than women (P=0.03, Figure 2C), while T5 Leptin levels were higher in women than men (P=0.03, Fig. 2C). No other significant difference was observed between Adipokine levels based on gender.

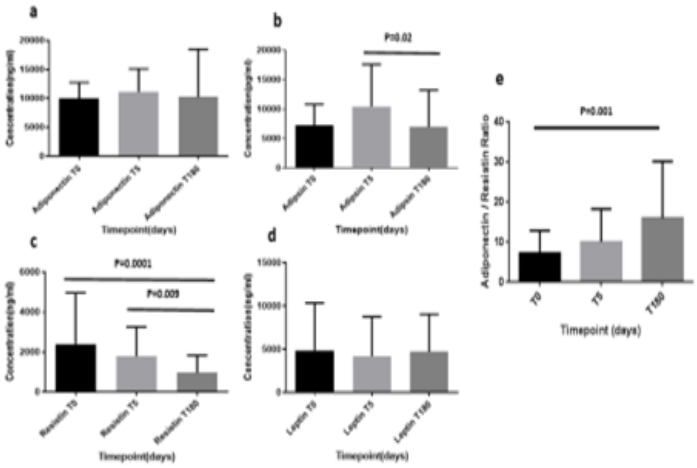

Fig. 1. Serum Adipokine levels in patients with MI at the time of admission to the hospital (T0), five days after admission (T5) and 180 days after MI (180). (a) Adiponectin levels (b) Adipsin levels, (c) Resistin levels, and (d) Leptin levels as well as Adiponectin to Resistin ratio (e) are shown

Table 2. Adipokine levels based on clinical histories of AMI patients in each time point

Subjects		No (%)	Adiponectin Mean (SD) (ng/ml ×10^3)			Adipsin Mean (SD) (pg/ml×10^3)			Resistin Mean (SD) (pg/ml ×10^3)			Leptin Mean (SD) (pg/ml ×10^3)		
			T0	T5	T180	T0	T5	T180	T0	T5	T180	T0	T5	T180
DM														
	Pos	9 (25)	10.1 (2.3)	12.9 (4.9)	10.3 (3.6)	6.6 (3.4)	14.1 (11.8)	7.8 (4.1)	2 (1.5)	2.1 (1.6)	1.5 (1.3)	3.1 (3.1)	3.8 (4.9)	5.02 (4.7)
	Neg	27 (75)	9.95 (2.8)	1.05 (3.5)	1.13 (8.6)	7.4 (3.66)	9.1 (4.3)	7.5 (6.6)	2.5 (2.8)	1.6 (1.4)	0.97 (0.7)	5.4 (5.9)	4.3 (4.5)	5.1 (4.3)
	P value		0.91	0.12	0.69	0.66	0.77	0.60	0.94	0.31	0.34	0.19	0.59	0.98
HTN														
	Pos	20 (55.6)	10.1 (2.2)	11.5 (4.4)	10.5 (5.5)	6.5 (2.9)	9.7 (2.7)	6.5 (3.8)	2.8 (3.2)	2.0 (1.6)	1.3 (1.0)	4.5 (5.3)	3.6 (3.0)	6.6 (4.9)
	Neg	16 (44.4)	9.8 (3.2)	10.5 (3.5)	12 (10.3)	8.1 (4.1)	11.3 (7.1)	8.8 (8.03)	1.8 (1.1)	1.5 (1.1)	0.7 (0.4)	5.2 (5.9)	4.9 (5.9)	3.3 (2.6)
	P value		0.88	0.60	0.92	0.24	0.42	0.53	0.47	0.51	0.25	0.88	0.88	**0.04**
HLP														
	Pos	9 (25)	9.2 (2.2)	12.4 (3.3)	12.8 (13.3)	8.07 (3.2)	15.0 (9.6)	9.3 (10.2)	1.7 (1.4)	1.9 (1.6)	0.8 (0.4)	4.7 (5.1)	4.6 (3.8)	6.4 (4.3)
	Neg	27 (75)	10.2 (2.8)	10.6 (4.1)	10.5 (4.9)	6.9 (3.7)	8.9 (5.4)	6.9 (3.7)	2.6 (2.8)	1.7 (1.4)	1.1 (0.9)	4.9 (5.7)	4.1 (4.8)	4.6 (4.2)
	P value		0.33	0.10	0.61	0.36	0.06	0.95	0.21	0.64	0.85	0.80	0.29	0.19
Smoking														
	Yes	22 (61.1)	10.6 (2.7)	11.9 (4.3)	12.7 (9.2)	7.6 (3.1)	11.1 (8.2)	8.7 (6.9)	2.4 (3.1)	1.5 (1.2)	1.2 (0.9)	3.1 (4.1)	2.7 (3.0)	5.7 (4.9)
	No	14 (38.9)	9.0 (2.4)	9.8 (3.0)	8.1 (2.9)	6.6 (4.2)	9.4 (5.2)	5.4 (3.4)	2.3 (1.4)	2.2 (1.8)	0.7 (0.3)	7.5 (6.3)	6.5 (5.6)	4.0 (2.4)
	P value		0.09	0.17	**0.04**	0.15	0.73	0.06	0.25	0.19	0.37	**0.01**	**0.01**	0.66
VD														
	CAD	6 (16.7)	12.1 (2.3)	11.7 (3.8)	10.1 (2.9)	7.9 (4.2)	12.6 (11.3)	5.5 (3.1)	1.8 (1.4)	1.1 (0.3)	0.7 (2.3)	4.5 (7.5)	4.4 (4.3)	6.2 (3.8)
	No VD	30 (83.3)	9.6 (2.6)	10.9 (4.1)	11.4 (8.7)	7.1 (3.5)	10.0 (6.2)	8.1 (6.5)	2.5 (2.7)	1.9 (1.5)	1.1 (9.1)	4.9 (5.1)	4.1 (4.6)	4.9 (4.4)
	P value		0.07	0.53	0.76	0.51	0.89	0.30	0.28	0.29	0.51	0.36	0.83	0.20
HR														
	Normal (60-100 bpm)	24 (66.7)	9.7 (2.9)	10.6 (3.8)	11.6 (9.1)	8.01 (3.7)	11.0 (7.4)	8.3 (6.8)	2.6 (2.9)	1.7 (1.4)	0.9 (0.7)	5.1 (5.8)	4.5 (5.1)	4.5 (4.0)
	Abnormal (ELSE)	12 (33.3)	10.5 (2.1)	12.1 (4.3)	9.9 (3.1)	5.6 (2.7)	9.2 (6.6)	5.5 (2.9)	1.9 (1.4)	1.9 (1.5)	1.2 (1.1)	4.3 (4.7)	3.5 (3.3)	6.6 (4.8)
	P value		0.43	0.19	0.86	0.06	0.46	0.27	0.73	0.48	0.65	0.81	0.91	0.25
SBP														
	Normal (<150 mmHg)	19 (53)	9.9 (2.9)	10.8 (303)	11.6 (10)	6.4 (3.1)	9.9 (7.2)	8.8 (7.8)	2.7 (3.2)	2 (1.6)	8.5 (8.3)	5.8 (6.7)	3.8 (4.2)	3.9 (2.5)
	Abnormal (ELSE)	17 (47)	10.1 (2.5)	11.1 (4.7)	10.8 (5.6)	8.2 (3.9)	11.0 (7.3)	6.5 (3.9)	2.0 (1.5)	1.5 (1.3)	1.3 (0.8)	3.9 (3.6)	4.6 (5.0)	6.3 (5.3)
	P value		0.66	1.0	0.71	0.21	0.51	0.49	0.66	0.14	**0.02**	0.75	0.49	0.22
RR														
	Normal (12-20 bpm)	16 (44.4)	9.9 (2.3)	11.1 (4.2)	10.8 (6.4)	5.6 (2.5)	8.8 (6.6)	6.03 (4.2)	2.5 (1.6)	1.7 (1.4)	1.1 (8.6)	6.07 (6.3)	6.1 (5.9)	4.5 (4.2)
	Abnormal (ELSE)	20 (55.6)	10 (3.02)	11.1 (3.9)	11.3 (9.01)	8.5 (3.8)	11.1 (7.4)	8.6 (7.02)	2.3 (3.1)	1.8 (1.5)	1.01 (8.5)	3.9 (4.6)	2.6 (2.1)	5.5 (4.3)
	P value		0.79	0.96	0.89	**0.03**	0.09	0.15	0.19	0.84	0.65	0.42	0.24	0.43
Total		36 (100)												

3.3. Concentration of Adipokines in the studied time points based on smoking status

Serum Adiponectin concentration at all three time-points was higher in smokers compared with non-smokers, but only at T180 the difference reached the significant level (P=0.04, Fig. 3A). The levels of Adipsin were also non-significantly higher in smokers than non-smokers (Fig. 3B). Serum Resistin levels varied over time and was only non-significantly higher in non-smokers at T5. Leptin levels were higher in non-smokers than smokers, but the difference reached a significantly higher level only at T0 and T5 (P=0.01 and P=0.01, respectively, Figs. 3C and D).

3.4. Correlation of Adipokine levels with risk factors and clinical and demographical characteristics of patients

In bivariate correlation analyses, serum Adipsin concentration at T0 was found to be significantly and inversely correlated with heart rate, respiratory rate and pulse rate (P=0.01, r=-0.39,

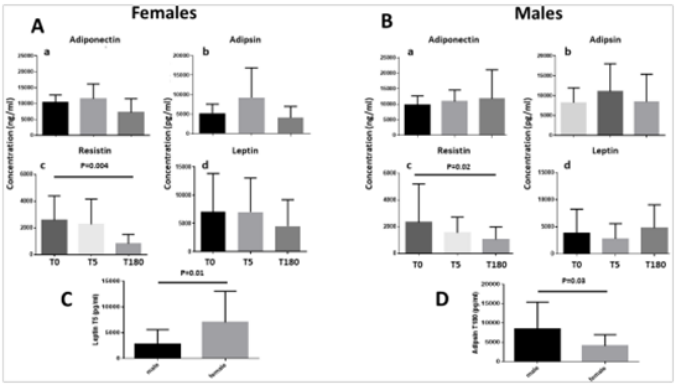

Fig. 2. Concentration of adipokines in the studies time points based on gender. Adiponectin (a), Adipsin (b), Resistin (c) and Leptin (d) in Females (A) and (B) Males. Differences in the Leptin T5 (C) and Adipsin T180 (D) between genders were statistically significant (P<0.05)

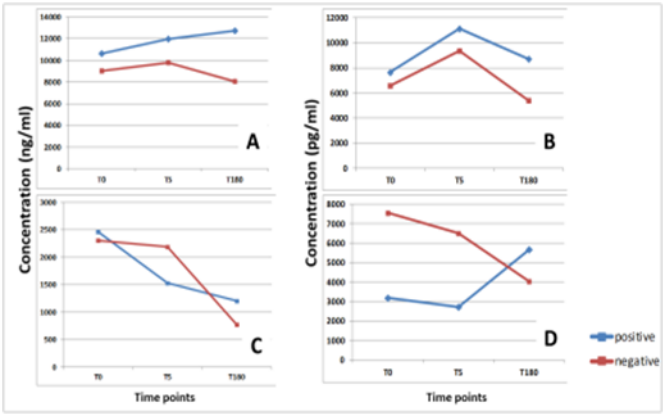

Fig. 3. Concentration of adipokines in the studies time points based on smoking status. Trends of changes in (A) Adiponectin, (B) Adipsin, (C) Resistin, and (D) Leptin in sera of patients

P=0.01, r=-0.40 and r=-0.35, p=0.03, respectively; Figs. 4A, 4B and 4C). Adipsin T5 levels were significantly and inversely correlated with age (r=-0.44, P=0.007, Fig. 4D). In addition, serum Leptin concentration at T5 and serum Resistin concentration at T180 were lower in those patients who had atrioventricular (AV) block (P=0.04 and P=0.05 respectively; Fig.5 A, B). Anteroseptal Hypokinesia correlated with serum Resistin level at T0 (P=0.02) and serum Adipsin level at T5 (P=0.02) while Leptin at T0 and T5 correlated with Anterolateral Hypokinesia (P=0.03 and P=0.004, respectively; Figs. 5 C-F).

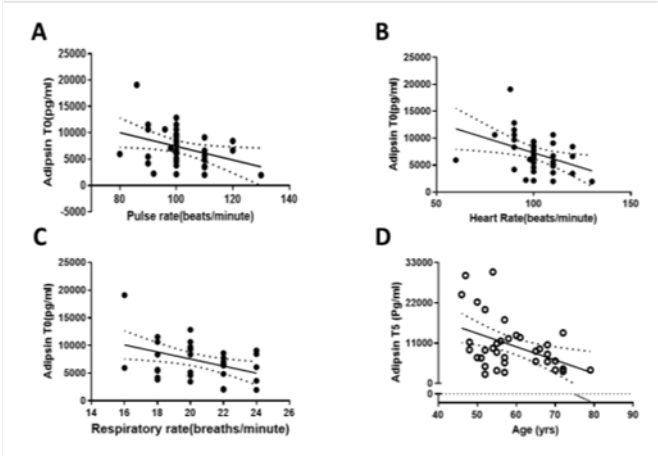

Fig. 4. Correlation of serum Adipsin concentration at T0 with heart rate, respiratory rate and pulse rate as well as Adipsin T5 with age in patients

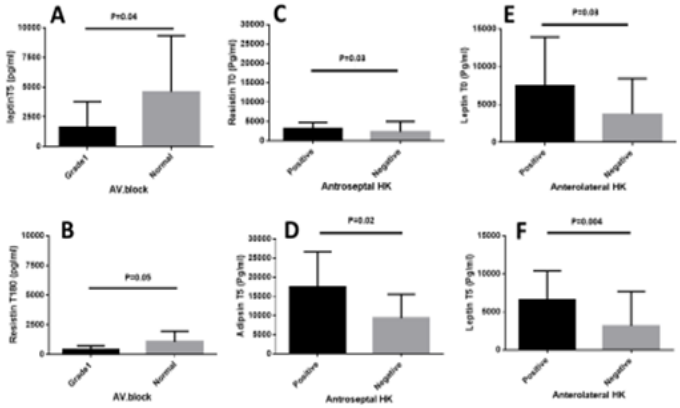

Fig. 5. Comparison of adipokine levels between patients. (A, B) Leptin levels at T5 and Resistin levels at T180 in patients with Atrioventricular (AV) block as compared to patients without block, C) Resistin T0 levels, D) Adipsin T5 levels, E) Leptin T0 levels and F) Leptin T5 levels in patients with Anteroseptal hypokinesia and those without

A significant negative correlation was observed between Adiponectin/Resistin ratio at T180 and Respiratory rate (r=-0.35, P= 0.048, Fig. 6A). Moreover, Adiponectin/Resistin ratio at T180 was significantly higher in patients with AV block grade-1 compared to those without AV block (P=0.025, Fig. 6B). Adiponectin/Resistin ratio at T180 was, however, lower in patients with Anterolateral Hypokinesia (P=0.024, Fig. 6C). Moreover, systolic blood pressure was found to be negatively correlated with serum Resistin (P=0.04, r= -0.34) and positively with serum Leptin concentrations at T180 (P=0.01, r=0.40, Fig. 7).

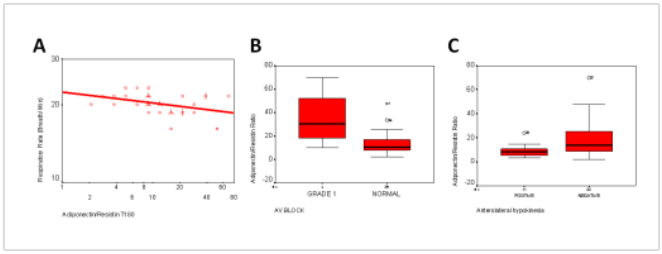

Fig. 6. Correlation between Adiponectin/Resistin ratio (at T180) and Respiratory rate (A), Atrioventricular (AV) block (B), and Anterolateral Hypokinesia (C) in patients with MI

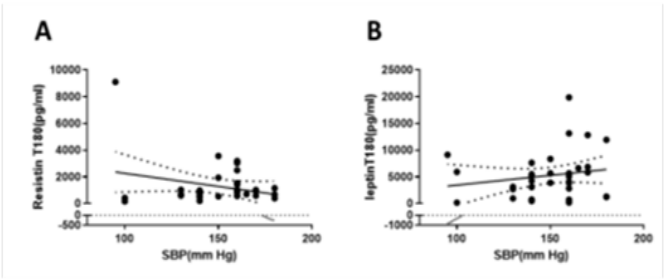

Fig. 7. Correlation of serum Resistin and Leptin concentrations at T180 with systolic blood pressure in patients

3.5. Comparison of Adipokine levels between patients based on their Acetylsalicylic Acid (ASA) and Statin treatments

We also compared the Adipokine levels between patients who had received ASA and/or Statin therapy in each time point. As shown in Table 3, there was no significant difference in the level of Adipokines between patients who received ASA and those who did not in any time point. For Statin, the only significant difference was observed in Resistin levels where those patients who had received Statin therapy had lower Resistin levels at the time of admission to the hospital (T0) compared to those who were not on Statin therapy (P=0.014) (Table 4).

Table 3. Adipokine levels in each time point based on ASA therapy

				ASA		
	Time point			T0	T5	T180
Adipokines	Adiponectin	P. value		0.074	0.077	0.432
		Mean ± SD (ng/ml ×10^3)	Pos. (N= 14)	11.1±2.3	12.08±3.6	13.1±11.4
			Neg. (N= 22)	9.2±2.7	10±4.1	10±5.1
	Adipsin	P. value		0.745	0.465	0.210
		Mean ± SD (pg/ml×10^3)	Pos. (N= 14)	7.3±3.5	9.8±7.9	10.2±8.8
			Neg. (N= 22)	7.1±3.6	10.8±6.7	6.1±3.1
	Leptin	P. value		0.236	0.626	0.389
		Mean ± SD (pg/ml×10^3)	Pos. (N= 14)	4.3±6.1	3.06±2.4	5.4±3.1
			Neg. (N= 22)	5.2±5.1	4.9±5.4	4.9±4.9
	Resistin	P. value		0.390	0.795	0.837
		Mean ±SD (pg/ml×10^3)	Pos. (N= 14)	2.5±3.6	1.9±1.5	1.2±1.1
			Neg. (N= 22)	2.3±1.6	1.7±1.4	0.9±0.6

Table 4. Adipokine levels in each time point based on Statin therapy

				STATIN		
	Time point			T0	T5	T180
Adipokines	Adiponectin	P. value		0.192	0.680	0.315
		Mean ±SD (ng/ml ×10^3)	Pos. (N= 5)	1.8±3.9	9.6±3.4	17.5±17.1
			Neg. (N= 31)	9.8±2.5	11.3±4.09	10.03±4.8
	Adipsin	P. value		0.200	0.086	0.050
		Mean ±SD (pg/ml×10^3)	Pos. (N= 5)	5.5±3.5	5.9±3.2	14.1±11.8
			Neg. (N= 31)	9.8±2.5	11.3±4.09	10.03±4.8
	Leptin	P. value		0.647	0.567	0.380
		Mean ±SD (pg/ml×10^3)	Pos. (N= 5)	3.9±4.7	2.5±1.8	4.5±4.1
			Neg. (N= 31)	5.03±5.6	4.4±4.8	4.8±4.3
	Resistin	P.value		**0.016***	0.423	0.379
		Mean ±SD (pg/ml×10^3)	Pos. (N= 5)	1.04±0.1	1.3±1.08	1.4±1.3
			Neg. (N= 31)	2.6±2.6	1.8±1.5	0.9±0.7

4. Discussion

It is shown that Adult cardiomyocytes produce Adipokines to protect the damaged cardiomyocytes (27). In our study, the serum concentrations of Adiponectin, Adipsin, Resistin and Leptin were measured in patients with MI at three different time points: during the first 12 hours of hospitalization (T0), five days after hospitalization (T5), and after six months of MI (T180). Our results indicated that Adipokines concentrations show various trends over time. Comparison of serum Adiponectin and Leptin concentrations at the three time points showed no significant changes over time. Resistin decreased significantly over the six-month follow-up and Adipsin levels fluctuated between time points. A previous study has shown that Resistin accelerates mechanisms involved in production of inflammatory cytokines (28, 29). Resistin increases p38 MAPK phosphorylation and NF-kappa B expression, however, anti-inflammatory treatments after MI, such as Aspirin, may decrease the effect of Resistin (28, 29). In our hands, however, there was no difference in the Resistin levels between those who were treated with Aspirin and those who were not in any of the time points. For Statin, however, we found that those patients who had received Statin therapy before MI had lower Resistin levels at the time of admission to the hospital (T0) compared to those who did not. This difference, however, should be interpreted with caution as the number of cases in the Statin treated group was very low (n=5). In accordance with studies in polycystic ovary syndrome (30) and acute coronary syndrome (31) we observed an increasing trend in Adiponectin to Resistin ratio after six months.

Resistin decrease started earlier in men compared to women after incidence of MI (Fig. 2). Previously, it was shown that Resistin is higher in women with diabetes than men with diabetes (32). A previous study on a small group of obese healthy individuals, has shown a higher level of Adipokines, including Resistin in females than males (33). Of note, Resistin is not associated with menstruation and does not change significantly during this period (34, 35).

In our study, there was a significant inverse relationship between smoking and serum Leptin concentration at earlier time points. This finding is not new and is in accordance with several previous studies (36, 37). However, there are contradictory reports that state otherwise in individuals with MI and atherosclerosis (38, 39). Knowing that after the first myocardial infarction, smokers have a shorter life expectancy because they may suffer from stroke at a younger age (40), and that smoking independently predicts major cardiovascular events, heart failure, and mortality (41), our results on the correlation of serum Leptin levels five days after MI as well as serum Adiponectin levels six months after MI with smoking may be important.

Interestingly, higher Adipsin levels at T0 were associated with decreased heart rate, decreased pulse rate, and decreased respiratory rate. A correlation between Adipsin and heart failure is reported (42), and Adipsin is suggested as one of the single predictors of heart failure (43). A recent study on a cohort of 370 patients with atherosclerosis showed that patients with higher Adipsin levels had a 4.2 fold increase in all-cause death and 2.4 fold increase in rehospitalisation (44). Interestingly, four of the five patients who developed MI during their course of follow-up and died because of MI had Adipsin levels higher than 400 ng/ml (44).

We also found that Leptin T5 and Resistin T180 were associated with atrioventricular block which is in accordance with previous studies showing the significance of these Adipokines in Atrial Fibrillation associated disorders (45-47).

We also found that Leptin levels were higher in patients with Anterolateral Hypokinesia in T0 and T5. Previous studies have shown that BMI correlates with left ventricular diastolic dysfunction (48), however, it decreases global hypokinesia of the heart (49). Bearing in mind that in addition to being an obesity related Adipokine, Leptin is also an inflammatory cytokine which contributes to other pathways and various diseases, the mechanistic involvement and significance of Leptin in Anterolateral Hypokinesia remains to be investigated (8, 10). Our results also showed that Anteroseptal Hypokinesia was associated with Resistin T0 and Adipsin T5 levels. These finding may be related to the cross-talk between heart adipose tissue and heart myocytes through these Adipokines similar to what is seen for Adiponectin (50). The lower ratios of Adiponectin/Resistin at T180 in patients with Anterolateral Hypokinesia may indicate a beneficial effect of Adiponectin on myocytes as previously suggested (50). Interestingly, the Adiponectin/Resistin ratio at T180 negatively correlated with respiratory rate at the time of admission, indicating the negative correlation of this index with MI prognosis.

Our results indicate that like other cytokines, Adipokines play their role in a network and may have both beneficial and harmful effect which is balanced by other Adipokines. Finding their interaction and their mechanism of action may pave the way for finding new cardiac biomarkers and/or drug targets.

Conflict of interest

The author(s) declare no conflicts of interest.

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